THE CANCER LETTER

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NCI STAFF WILL RECOMMEND THAT COMPREHENSIVE RECOGNITION BE WITHDRAWN FROM COLORADO CENTER

NCI staff will recommend to the National Cancer Advisory Board at the Board's February meeting that recognition as a comprehensive cancer center be withdrawn from the Colorado Regional Cancer Center.

The staff recommendation probably will go first to the NCAB Subcommittee on Centers & Construction, with the subcommittee then reporting its findings to the full Board. A final decision on removing Colorado from the list of recognized comprehensive centers will be up to NCI Director Vincent DeVita, since the NCAB role is advisory only.

(Continued to page 2)

In Brief

SPECIAL MEETING TO REVIEW VIRAL ONCOLOGY ASKED BY DCCP BOARD; BCTF BUDGET: $8 MILLION

SPECIAL MEETING of NCI's Div. of Cancer Cause & Prevention Board of Scientific Counselors to review the institute's entire intramural and extramural efforts in viral oncology was requested by the Board at its recent meeting. Board member James Watson agreed with Brian Henderson and Bernard Weinstein that such a review would be useful. NCI's support of viral oncology was "very successful," Watson said. "It got something going, and the field took off. There are other areas that haven't taken off and should have." . . . **BREAST CANCER** Task Force budget is $8 million, not $12 million as reported in **The Cancer Letter** Oct. 17. Also, NCI Director Vincent DeVita's estimate that the institute supports $47 million in breast cancer research probably is high. The BCTF budget is divided $5 million for grants, $3 million for contracts, and all are reviewed either by DRG study sections or NCI review committees. . . . **NITRITES, ALTERNATIVE** curing agents will be discussed at a meeting of a National Academy of Sciences-National Research Council committee meeting Jan. 22, 1981, in Washington. Individuals and organizations are invited to submit information on health risks and benefits of nitrites and nitrates and on the status of research on alternatives. The committee is especially interested in obtaining scientific information not in the published literature. Material should be submitted, in at least two copies, to Robert Mathews, NAS, (WG-1003), 2101 Constitution Ave. NW, Washington D.C. 20418, no later than Dec. 5. . . . **ONCOLOGIC DRUGS** Advisory Committee of FDA will discuss NDAs for ifosphamide (Mead Johnson) and vindesine (Eli Lilly) at its meeting Nov. 7. . . **ERKKI RUOSLAHTI** has been named scientific director of the La Jolla Cancer Research Foundation. He has been associate director for science since 1979, previously was director of immunobiology at City of Hope National Medical Center.

NCI REJECTS CRCC REQUEST FOR ANOTHER DELAY IN COMPREHENSIVENESS REVIEW

(Continued from page 1)

However, it was the Board which established criteria for comprehensive recognition and procedures for withdrawing recognition. It does not seem likely that DeVita would reject the Board's advice on that issue.

CRCC has been in trouble since it lost its core grant nearly two years ago. The NCAB subsequently revised its criteria or "characteristics" for comprehensive centers to include the provision that loss of a core grant would be a signal that a center may no longer meet the test of "comprehensiveness."

NCAB required that a center losing its core grant would have one year in which to apply for a new one. If no such application is submitted within the year, an NCAB site visit team would review the center.

CRCC did not apply for a new grant within the year, and still has not. NCI Centers Program staff attempted to schedule an NCAB site visit last spring, but CRCC asked for a postponement to July, and then again to November.

Finally, when CRCC asked for another postponement, NCI balked. Staff members felt that the NCAB requirements had not been met and that they have no choice other than to withdraw recognition.

J. Brian O'Toole, acting director of CRCC, acknowledged that if a Board site visit were to be held in November, "we would not meet the test of comprehensiveness."

CRCC is one of two comprehensive centers (Illinois Cancer Council is the other) organized as a consortium, with more than 20 institutions as members. The consortium concept has not worked well, in Colorado. Since loss of the core grant, an attempt has been made to reorganize with less emphasis on the consortium and a larger role for the Univ. of Colorado Health Sciences Center. The reorganization process has been delayed by a number of factors, but O'Toole, who moved up from deputy director to acting director only last month, feels that progress has been made.

"Essentially, we are looking for a time extension," O'Toole said. "We are gaining momentum, and within six to eight months, we will see improvement."

Members of the consortium in general are supporting the reorganization, with the university assuming more power. M. Roy Schwarz, new dean of the medical school, is firmly backing the reorganization and supports the school's participation as the leading component of a major cancer center.

O'Toole said that CRCC is asking to be placed "on inactive status" as a comprehensive center rather than have the recognition formally withdrawn. "To lose the comprehensive designation now would be the kiss of death locally, more so even than nationally."

NCI executives have dreaded the possibility that they someday might have to take away the prestigious comprehensive designation from a center. They are aware of the devastating impact such a loss could have on a center's ability to attract local and state support, to secure cooperation of other institutions within its region, to keep and recruit quality people. Those are the chief advantages of comprehensive status; to lose that status is worse than never having had it in the first place.

CRCC's location will make withdrawal of comprehensive recognition even more difficult. The East Coast, Southeast, West Coast and Great Lakes regions are reasonably well covered by comprehensive centers. There are no comprehensive cancer centers between Houston and Seattle, nor between Los Angeles and Chicago. Diagonal lines on a map connecting those cities intersect in the middle of Colorado, placing Denver near the geographic center of about one third of the United States which is not served by a comprehensive cancer center.

With the attempts to establish comprehensive centers in Missouri and Kansas apparently shelved, the impact of withdrawing recognition to CRCC is even more severe.

The geographic factor probably was the primary reason for extending recognition to CRCC in the first place. NCAB members and NCI staff admitted that CRCC was not close to meeting all the characteristics of a comprehensive center, but they hoped that in time it would. The Board review of all existing comprehensive centers, completed in 1978, noted those deficiencies (and others elsewhere). Although some progress had been made, failure to get the core grant approved and funded in effect moved the timetable far forward.

"The real problem," one person close to the center told *The Cancer Letter,* "Is that they have never been able to get a solid, major commitment from the university. That is really all that is needed. If the university gets behind the cancer center and makes the kind of commitment, of resources, space and authority, that other universities have made, everything else will fall into place."

The university appears to be ready now to make that commitment, but it may be too late to prevent loss of comprehensive status. "We have to face up to the fact that a comprehensive center does not now exist in Colorado," an NCI executive said. "If they can get their act together, get a new core grant funded, then in a year or two they can request recognition again."

RECOMPETITION FOR $8 MILLION IN DCT CONTRACTS APPROVED BY COUNSELORS

The Board of Scientific Counselors of NCI's Div. of Cancer Treatment approved the recompetition of $8 million in existing contract supported programs,

nearly all of which will be competed through RFPs which will be issued during the 1981 fiscal year.

One of the projects which has been funded by contracts—the multi-institution study on therapy of patients with colon and rectal cancer through the Gastrointestinal Cancer Study Group—was approved for recompetition as contracts for three year awards. DCT staff had requested approval for five years. The Board approved three years by contracts with an additional two years to be funded through cooperative agreements provided the participating institutions have demonstrated sufficient patient accrual at that time. Estimated first year award is $637,000.

Eight institutions originally participated—Albany Medical College, Mayo Clinic, Sidney Farber Cancer Institute, New York State Dept. of Health, Univ. of Miami, Mount Sinai School of Medicine, UCLA, and Georgetown Univ. Farber and UCLA subsequently dropped out because of lack of patient accrual.

The studies included a randomized four arm comparison of postoperative chemotherapy (5-FU and methotrexate), immunotherapy (MER), and chemo-immunotherapy compared to a surgery only control group for treatment of colon cancer. To date, there are no clear differences between any of those groups, although the surgery only group has produced results superior to those for historical controls.

Reports on concept reviews by the boards of scientific counselors of NCI divisions provide readers of *The Cancer Letter* with advance notice of the institute's spending plans which will show up in RFPs and RFAs in subsequent months. Those interested in participating in programs approved by the BSCs should be aware of two points:

• The dollar figures cited as first year awards for each contract program are NCI staff estimates only and should not unduly influence development of proposals. These will be competitive awards and cost is a factor in selection of successful proposals.

• In no event should proposals be written until requests for proposals (in the case of contracts) or requests for applications (for grants and cooperative agreements) are available. Announcement of their availability will appear in *The Cancer Letter.*

The best results, apparently so far, are turning up in the comparison of postoperative chemotherapy, radiation therapy and combined chemo-radiotherapy with a surgery only control group in resectable rectal carcinoma. The control arm was closed last February when it emerged as significantly inferior, with 42 percent recurrence. The radiotherapy group has had 32 percent recurrence, chemotherapy only (5-FU and MeCCNU) 39 percent, and combined, 21 percent. (Details of this study are reported in the October issue of *The Clinical Cancer Letter.)*

A new colon adjuvant study was initiated in late 1979 and compares surgical adjuvant systemic 5-FU plus hepatic irradiation with a surgery control group. This study targets therapy at an organ likely to be a site of relapse.

The Board approved recompetition of another project presently being carried out by contracts with several institutions, and went along with DCT's request to convert the mechanism to quick reaction work orders, or task orders. This is for pharmacological studies of antitumor agents presently being performed by Arthur D. Little Inc., Southern Research Institute, Univ. of Texas System Cancer Center, Ohio State Univ., and Mount Sinai School of Medicine. Estimated first year award was $1.6 million. DCT staff narrative describing future plans for the project:

After selection of the master contracts for a period of three years, individual work orders relating to specific pharmacological tasks will be competitively awarded to successful offerors from a panel of master contractors. It is felt that focusing on specific pharmacological tasks as work orders will permit the optimal utilization of available resources and that competition for the individual tasks will permit selection of the optimum skill-mix needed for a particular project. Specific work orders may consist of projects involving the development of analytical methodology for a new agent, determination of the physiological distribution and pharmacokinetics of an agent in several species of animal and in the clinic, when appropriate, pharmacokinetic studies of new formulations of experimental agents, studies on the stabilities of new agents, studies on plasma protein binding of selected drugs, studies on the duration of biochemical effects of drugs, studies on discrete localization of labeled drugs in vivo by radioautography, studies on the physiological effect of agents which may correlate with pharmacological measurements of drug concentrations, studies of the formation and structure of metabolites of new agents in vitro and in vivo and limited studies on the synthesis and pharmacological properties of putative metabolites. It is expected that master contractors will be able to conduct all or most of these studies as may be required by the individual work orders and will conduct the work in a prompt and efficient manner. It is further anticipated that depending on the project the time for these studies could range from a few weeks up to a year for the more complex tasks.

Other projects approved for recompetition by the Board:

Planning and analytical support services. Estimated first year award of $316,000 on a three year contract. The narrative:

The current contractor [CDP Associates] has provided comprehensive planning and analytical support services, and general planning, documentation and logistical support for the division and its Board of Scientific Counselors. A few examples of these efforts were the analytical data developed in part by the contractor that led to the formation of an ad hoc study section to review clinical grants; conference and documentation support for meetings and workshops related to meetings held by subcommittees of the Board, namely Biological Response Modifiers and the Radiation Oncology (ROCS). The contractor also provides general conference support for meetings/workshops held by the division including a recent conference on head and neck cancer and provides documentation support for the materials needed for the board meetings. It is anticipated that similar tasks and skills will be required by the new contractor.

Phase 1 and 2 studies of new anticancer agents. Estimated first year award is $1.5 million on five year contracts.

Present contractors are Sidney Farber Cancer Center, Univ. of Kansas, Mount Sinai, Univ. of Vermont, Univ. of Wisconsin, Georgetown Univ., Mayo Clinic, Memorial Sloan-Kettering, M.D. Anderson, and Wayne State Univ. This group has been the core of DCT resources for phase 1 evaluation of all new anticancer drugs. They have demonstrated that complete studies can be done at one institution in a short time and that qualitative and quantitative toxicity can be confirmed at several institutions. The single agent phase 2 studies in selected panel tumors have been designed to fill disease gaps in the evaluation of the new drugs.

Drug distribution and protocol monitoring system. Estimated first year award, $165,000 on a five year contract. The narrative:

The Drug Distribution and Protocol Monitoring System is a computer software system used by the Investigational Drug Branch to verify the accuracy of drug requests and to insure that clinical protocols using these drugs conform to FDA regulations. The current contractor [Value Systems Engineering] has been responsible for operating, maintaining, and modifying this system as necessary. In addition, the contractor prepares reports to assist the IDB in its drug regulatory responsibilities, including reports of drug shipments by protocol and investigator, the protocol information file (an investigator protocol listing), drug monitor reports, cooperative group distribution reports, specialized drug reports, and other special reports which are generated as necessary. The contractor also coordinates the re-registration procedure for all investigators receiving investigational agents, as required by the FDA. Future plans include development of a system to review protocol drug needs in conjunction with available drug supplies.

Statistical support for the Gastrointestinal Tumor Study Group. Estimated first year award of $270,000.

DCT had asked this be recompeted for five years as a contract (Emmes Corp. is the present contractor), but the Board felt it should be a cooperative agreement, since funding of all clinical research groups will be converted to that mechanism (**The Cancer Letter**, Oct. 10). The contract was approved for recompetition as a contract for one year, and will be incorporated into the GITSG cooperative agreement after that.

Clinical study of photoradiation therapy. Estimated first year award of $125,000.

Again, DCT had asked for recompetition as a contract, but the Board voted to convert it to a cooperative agreement, approving an extension of the contract for one year if needed. Roswell Park Memorial Institute is the present contractor. The narrative:

We intend to award two contracts which will be sequels to pioneering work at Roswell Park using hematoporphyrin derivative (Hpd) activated by visible light. These derivatives are being investigated for the control of solid malignancies. This modality is based on the ability of Hpd first, to accumulate and be retained in malignant tissue to a greater degree than in some normal tissues and second, to produce singlet oxygen when activated by visible light thus producing a cytotoxic effect. This latter property is common to a wide range of materials. However, its combination with tumor localizing ability is comparatively unique. Many other porphyrins have been examined as potential tumor photosensitizers in animals, but none has been found as effective as Hpd. To date, most patients treated have had cutaneous and/or subcutaneous lesions in which Hpd was photoactivated by externally applied red light. Typically, Hpd is injected in doses of 2.5 to 10 mg/kg followed 3 to 10 days later by exposure of the lesions to activating red light at doses ranging from 18 to 700 joules. Light sources used include a laser, an xenon lamp with appropriate filtration, and a bank of specially designed fluorescent lamps. A variation of this technique is being investigated as a diagnostic tool. Violet light is used to excite red fluorescence of Hpd in tumors. While red light penetrates tissue to a greater extent than any other visible wavelength, its effective penetration depth is approximately 2 cm—thus severely limiting the potential of externally applied radiation. The potential of PRT can be extended by combinations of laser and fiberoptics technology. Lasers can provide intensity of appropriate wavelength (625-640 nm) such that transmission through glass fibers allows light delivery through various endoscopes or inserted needles.

Future plans include phase 2 studies of soft tissue recurrence of breast carcinoma; systematic investigation of dose fractionation; larger lesions will be tested with interstitial PRT using specially adapted light fiber systems in conjunction with laser systems. PRT will be extended to tumors accessible either intraoperatively or endoscopically. Adenocarcinomas of the stomach, esophagus, pancreas, head and neck, etc., are of primary interest.

Provision, maintenance and transfer of tumored laboratory animal models for investigation. Estimated first year award, $300,000 on a three year contract. The narrative:

Currently, the majority of the tasks involve holding of normal animals prior to experimental processing at NIH. The contractor [Litton Bionetics] provides transportation of the animals between the facility and NIH on a daily basis. The Litton staff provides housing, watering, and feeding of the animals. In addition, animals which have been experimentally manipulated are observed by the Litton staff who perform mortality checks. The staff has the responsibility of notifying individual investigators when their experimental animals are sick or have expired. Additionally, the facility provides housing for animals involved in ongoing experimentation. The staff provides necessary assistance to the individual investigators for experiments performed at the facility.

Litton provides animal rooms which meet government regulations for containment of hazardous substances. These containment rooms are used for carcinogenesis experiments where animals are exposed to actual or potential carcinogens for induction of experimental tumors. There are no such containment facilities in the Clinical Center which would permit carcinogenesis experiments on small animals to be carried out without the potentially hazardous exposure of personnel to chemical substances.

Preclinical canine bone marrow transplantation and immunotherapy studies. Estimated first year award, $220,000 on a three year contract. The narrative:

The present contractor is Hazleton Laboratories Inc. We are completing studies relating to the expansion of peripheral blood stem cells during recovery from chemotherapy given at conventional doses. We have found that complete hematopoietic reconstitution occurs following total body irradiation (900 rads) when dogs are infused with peripheral blood mononuclear cells. These data have shown that pluripotent stem cells exist in the peripheral blood in numbers adequate to effect hematopoietic reconstitution following ablative therapy.

Numbers of committed myeloid precursor cells in collections of peripheral blood mononuclear cells from lung cancer patients are amplified during the recovery phase from conventional dose therapy. A dog model has been established in which this phenomenon of chemotherapy-induced amplification of committed myeloid precursor cells has been duplicated. We have used this model to show that it is possible to generate complete hematopoietic reconstitution using these amplified populations of purified blood mononuclear cells following 900 rads of total body irradiation. The number of peripheral blood mononuclear cells which are required under such circumstances is 1/20 the dose in untreated animals. These data show that the chemotherapy induced amplification of precursor cells in dog and man is associated with amplification of pluripotent stem cells as well. These studies continue.

In addition, we have also explored the hemoperfusion-staph A protein model of Terman and found that this treatment can

be associated with regression of anaplastic mammary adenocarcinoma in dogs in our laboratory. We are, therefore, looking at additional animals with osteogenic sarcoma and mammary adenocarcinoma in order to establish the efficacy of the technique and to develop the technical knowledge to prepare for trials in man.

We have begun an investigation of the effects of extracorporeal immunoadsorption in spontaneous canine tumors. The use of inactivated S. aureus would provide a mechanism for nonspecifically removing circulating immunosuppressive complexes and free antibody. The initial goal was to achieve tumor cytoreduction; further investigation of the mechanisms involved is planned.

Our plan is to try to develop a more suitable immunoadsorbant column than one loaded with bacteria, with the eye of using this in man. In addition, we will continue to test the determinants of response in the dog model, and test whether a response is dependent on the removal of immune complexes and whether these immune complexes contain antitumor antibodies. Finally, we will test whether such columns have antibodies specific for tumor antigens.

Synthesis of natural product analogs as potential anticancer agents. First year award, $215,000 on a three year contract. The narrative:

Present contractor is Bristol-Myers. This contract is the only mechanism available for the synthetic modification of natural products. An essential prerequisite for this contract is the ability to synthesize all compounds in quantities adequate for preliminary screening (1-3 g.). The contractor has synthesized compounds of different natural product classes. They have synthesized more than 40 tricothecanes related to anguidine. Two of these have shown activity greater than the parent compound and have been selected for complete tumor panel testing. A selected number of maytansine, nogalamycin and sterigmatocystin analogs were also synthesized. These areas were discontinued because of lack of sufficient activity in the initial screens. Some developmental work on acivicin was also undertaken.

We plan to develop a practical method for the steriospecific cycloaddition of alkenes to nitrile oxides as a route to the synthesis of novel isoxazoline antibiotics related to acivicin. It is expected that these modifications may result in compounds with less CNS toxicity. Another area, currently under review by the Analog Development Committee, is the pyrrolobenzodiazepine antibioetics related to anthramycins and neothramycins. Other specific areas will be assigned based on changing program needs.

Plant tissue culture and fermentations as a source of antineoplastic agents. First year award, $100,000 on a three year contract. The narrative:

Present contractors are the Univ. of British Columbia and Kyowa Hakko Kogyo, but only one contract will be awarded in the recompetition. Plants which are sources of compounds of high interest to DCT are assigned to the contractors and viable tissue is provided as either seeds or growing plants. The contractor must develop conditions to grow the plant cells in callus culture or solid media and then in suspension culture. This involves extensive experimentation with various growth media and plant hormones. Cultures having rapid enough growth for further development are then assays for their ability to produce the compounds of interest. This is generally done by cytotoxicity assays since chemical assays are not sensitive enough to detect the very low levels of active substance. Radioimmune assays are developed to specifically detect the compounds of interest but are not yet avilable. Cultures showing promise are scaled up in either shake flasks or fermentors to obtain sufficient material for chemical isolation and identification. Extensive experimentation is necessary to get satisfactory growth conditions. Cultures which are proven to produce the desired components (these are all heterogeneous cultures) are subjected to cloning and the various pure strains obtained are again examined for growth characteristics and production to finally obtain a pure strain which grows well and is a good producer. Such strains will be adapted to fermentation conditions in larger fermentors and will be used to produce the compounds of interest in quantities to meet program needs.

During the first 18 months of the contract seven plants were investigated which are sources of agents of interest to NCI. All of these plants have been successfully cultured on solid media and in suspension culture. Five of the seven plants have been found to produce biologically active substances in culture. In three plants, cepthalotaxus, baccharis and putterlickia the active materials have been identified as being either the desired active components (homoharringtonine, baccharin and maytansine respectively) or very closely related compounds. Positive identification could not be made due to the small scale on which the cells were cultured. One plant, tripterygium wilfordii, has been definitely shown to produce tripdiolide of a level equal to or better than that occurring naturally in the plant. Radioimmune assays are being developed which should be sensitive enough to detect the desired active principles in individual cultures which should speed up selection of producing strains.

Work is ongoing to clone multiple lines of tripterygium cells and to isolate a stable cell line with good growth and tripdiolide production characteristics. In the next three years of this contract emphasis will be placed on isolation of useful cell lines from all the promising plants and development of large scale fermentation conditions to produce the desired substances in suitable quantities to meet DCT needs for these drugs. The results from the work to date have been very promising and the goal of obtaining one or more of these drugs by plant cell fermentation in the next three years seems attainable.

Preparation of plant extracts. First year award, $125,000 on a three year contract. The narrative:

The present contractor is Raltech Scientific Services Inc. This project is a service contract charged with preparation of plant extracts for screening from the plant materials collected by USDA. Plant materials are received, stored, ground and extracted according to standard protocols established by NCI. The extracts are then assigned screening code numbers and sent to screening contractors for evaluation of in vivo and in vitro activity. Data on the names, families, locations and seasons of collection, type of extract prepared and screening code numbers are entered on appropriate forms and transferred to NCI for entry into permanent computerized records of plants screened. When a plant extract shows initial activity the plant is re-extracted and a sample prepared for confirmation testing. The project is an essential link in the development of new antitumor agents from plants.

Due to a DCT program decision to cut input to the primary screen in favor of more secondary (tumor panel) testing the acquisition of plants for screening has been reduced to about 2,500 per year and the number of extracts to be prepared under this contract has been similarly reduced. This reduction in output should enable the work to be successfully performed at the same dollar level in spite of salary increases, inflation and, particularly, large increases in solvent costs which are a major contract cost.

Biochemical and biological characterization of antitumor agents. Estimated first year award, $150,000 on a three year contract. The narrative:

Present contractor is Arthur D. Little Inc. The primary objective has been to provide basic information on the cytotoxic and biochemical effects of antitumor agents being considered for development toward clinical trial. The studies were designed to provide clear leads as to how the agents exert their

effects, and to provide enough information for enlightened decision-making. The studies were not intended to elucidate definitively the mechanism of action of a developmental drug. This contract has been the sole resource available to DCT for obtaining preliminary biochemical information on new agents in a timely manner.

The current project plan has been designed so that studies conducted under the new contract will be tailored to the individual compound. The emphasis will be on providing basic biological/biochemical data on new agents in a timely manner so that the information can be used to aid the decision-making process and to help set priorities for developing agents toward clinical trial. The contract will be used (1) to answer specific biological questions on potential new antitumor agents that are raised by the Decision Network Committee; (2) to obtain information on the biochemical properties of analogs at the request of the various analog coordinating groups; and (3) to establish whether agents with novel chemical structures are also unique with respect to their probable mechanism of action.

Storage and distribution of clinical drugs. Estimated first year award, $580,000 on a five year contract. The narrative:

The present contractor, Flow Labs Inc., is currently processing an average of 50 shipments per day. All orders are processed the same day that the order is received from the Investigational Drug Branch. The personnel has been available on weekends for processing of emergency shipments. The computer processing of clinical drug request forms and delivery of routine reports has functioned smoothly. Additionally, creation of new files and programs, modifications to existing files as well as numerous special queries have been performed satisfactorily. During 1979, a decision was made to supply delta-9-THC, a schedule I substance. Flow built a vault to hold this substance within one month after receiving the necessary funding. This contractor has been extremely responsive to the needs of the program and performance has been exemplary.

The workscope of the recompeted contract will involve the receiving of all clinical drug items, proper storage of these items, the packaging and distribution of them to authorized clinical investigators, and the creation and maintenance of adequate computerized records of all transactions. The drug storage area will provide controlled conditions to facilitate optimal storage of all formulated products. In addition, a DEA licensed, highly secure storage facility for scheduled substances providing an adequate amount of refrigerated space will be necessary. The contractor will ship formulated products domestically and to many countries throughout the world. Additionally, adequate records (both manual and computerized) will be maintained to meet all of the requirements of NCI, FDA and DEA. These records will include receiving and distribution, quarantine, expiration, sampling required and a variety of routine and special activity reports as required. It should be pointed out that the increased funding level is based on both inflation and the significant impact that the storage and distribution of delta-9-THC will have upon this contract.

Induction, biological markers and therapy of tumors in primates. Estimated first year award, $480,000 on a three year contract.

Hazleton Laboratories is the present contractor. "This is a national resource for the study of carcinogenesis of antitumor agents," Developmental Therapeutics Program Director Vincent Oliverio said. The narrative:

The adverse and potential carcinogenic effects of 27 compounds including several antitumor drugs are being evaluated. Nine compounds including procarbazine, methyl-nitrosourea and aflatoxin B_1, have been shown to be carcinogenic in monkeys. Alpha-fetoprotein has been found to be a useful marker for diagnosis and following therapy. A contrast material was developed for CAT scanning of the liver and spleen. These 27 compounds and several other antitumor agents will continue to be examined for adverse effects including carcinogenicity. Studies using nucleophiles and other approaches for prevention of the carcinogenic effect of antitumor agents will be pursued. The tumor bearing monkeys will continue to be used for therapy and for development of diagnostic tests including contrast material to enhance CAT scans.

In vitro screening program. Estimated first year award, $324,800 on three year contracts. The narrative:

Present contractors are Arthur D. Little, Univ. of Miami and Univ. of Wisconsin. All new plant and animal products are prescreened in both in vitro and in vivo assays. Those demonstrating in vitro efficacy in the prescreen undergo limited fractionation in an effort to concentrate the active moiety for testing for in vivo activity. All natural products that demonstrate in vivo activity are tested in vitro assays so that if sufficiently cytotoxic, the fractionation testing can be carried out by in vitro assays. This provides a more rapid assay and thus better turnaround time for the fractionating chemists. The in vitro assay costs only about one-third that of an in vivo assay. When feasible then, because it is both faster and less expensive, an in vitro assay is utilized for the fractionation or isolation of the active component of natural products. It is anticipated that the need for this type of project will continue. Currently other in vitro assays are being studied for incorporation into the program. For example, the Univ. of Miami has recently established a rat glióma (astrocytoma) assay system. This assay is sensitive to materials that either inhibit the synthesis or formation of microtubules. It is proposed that additional in vitro systems will be added to this program which will identify materials with varying mechanisms of action in an effort to select new classes of anticancer agents.

Additional contracts approved for recompetition will be described in next week's issue of ***The Cancer Letter.***

NCI CONTRACT AWARDS

Title: A resource to continue the development of detailed methods and protocols for carcinogenesis screening using cell culture assays by the NCI Carcinogenesis Testing Program

Contractor: Arthur D. Little, $324,732.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR NOV., DEC., FUTURE

Clinical Cancer Education Committee—Nov. 5-6, NIH Bldg 31 Rm 4, open Nov. 5 8:30–9:30 a.m.

25th Annual Clinical Conference—Gastrointestinal Cancer—Nov. 5-7, Shamrock Hilton Hotel, Houston.

39th Annual Meeting Japanese Cancer Assn.—Nov. 5-7, Tokyo.

Cancer & Risks—Nov. 5, Miami Valley Hospital, Dayton.

Pancreatic Cancer Review Committee—Nov. 5, Ambassador West Hotel, Chicago, open 8:30–10 a.m.

Advances in Head & Neck Oncology—Nov. 6, Roswell Park continuing education in oncology.

Prostatic Cancer Review Committee—Nov. 6, Omni Hotel, Atlanta, open 8–8:30 a.m.

Diet, Nutrition & Cancer— Nov. 6, National Academy of Sciences, 10 a.m.–3 p.m.

Cancer Special Program Advisory Committee—Nov. 6-7, Bethesda Marriott Hotel, open Nov. 6, 9–10 a.m.

Cancer Prevention & Screening—Nov. 7-8, Holiday Inn—Union Square, San Francisco.

FDA Oncologic Drugs Advisory Committee—Nov. 7, Parklawn Bldg, Conference Room A, 9 a.m., all open.

Prevention of Colorectal Cancer—Nov. 8, 13th annual special pathology program, Shamrock Hilton, Houston.
Pain Management in Cancer Patients—Nov. 8, Univ. of Delaware, Newark, Dela.
Cancer Clinical Investigation Review Committee—Nov. 10-12, NIH Bldg 31 Rm 6, open Nov. 10, 8:30–9:30 a.m.
President's Cancer Panel—Nov. 12, NIH Bldg 31 Rm 11A10, 10 a.m., open.
Cancer Centers Support Review Committee—Nov. 13-14, NIH Bldg 31 Rm 6, open Nov. 13, 8:30–10 a.m.
Bone Marrow Transplants—Nov. 13, Roswell Park continuing education in oncology.
Committee on Cytology Automation—Nov. 13-14, NIH Bldg 31 Rm 10, open Nov. 13, 8:30 a.m.–5:30 p.m., Nov. 14, 8:30–10:30 a.m.
Comprehensive Cancer Rehabilitation & Its Vocational Implications—Nov. 13-15, Fort Magruder Conference Center, Williamsburg, Va., sponsored by Va. Dept. of Rehabilitative Services and MCV/VCU. Phone Keith Wright, VCU, 804-257-1132.
Caring for the Care Giver—Nov. 14, St. Paul Hospital, Dallas.
Leukemia Update—Nov. 14, Cornell Medical School, sponsored by Leukemia Society of America and Cornell.
Radiological Society of North America—Nov. 16-21, Dallas.
National Cancer Advisory Board—Nov. 17-19, annual program review, NIH Bldg 31 Rm 6, 8:30 a.m. Nov. 17, 9 a.m. Nov. 18 and 19, all open.
Relation of Carcinogen Action on DNA to Cell Transformation—Nov. 18, Jefferson Medical College, Philadelphia.
2nd Asia & Oceania Congress of Nuclear Medicine—Nov. 14-28, Manila.
7th UICC Training Course in Cancer Research—Dec. 1-12, Walter & Eliza Hall Institute, Melbourne.
Large Bowel Cancer Review Committee—Dec. 4-5, Prudential Bldg., Houston, open Dec. 4, 7:30-8 p.m.
Metastasis: Pathobiological Aspects with Some Illustrative Clinical Examples—Dec. 4, Roswell Park continuing education in oncology.
2nd Annual Patient Education Research Seminar—Dec. 6-7, Univ. of California (San Francisco), Cole Hall. Contact UCSF, Continuing Education in Health Sciences, 1308 3rd Ave., San Francisco 94143, phone 415-666-2894.
Clinical Cancer Program Project Review Committee—Dec. 8-10, NIH Bldg 31 Rm 6, open Dec. 8, 8:30–10 a.m.
President's Cancer Panel—Dec. 9, NIH Bldg 31 Rm 9, 10 a.m., open.
Breast Cancer Task Force—Dec. 9-10, NIH Bldg 1 Wilson Hall, 8:30 a.m. both days, open.
Cooperative Group Chairmen's Committee—Dec. 16, NIH Bldg 31 Rm 9, open 9 a.m.–4 p.m.

FUTURE MEETINGS
Gynecologic Oncology Group—Jan. 8-10, 1981, semi-annual national business meeting, Miami.
UCLA Jonsson Comprehensive Cancer Center Inaugural Scientific Symposium—Jan. 24, 1981; NCI Director Vincent DeVita and Henry Kaplan of Stanford will be the visiting speakers.
34th Annual Symposium on Fundamental Cancer Research—March 4-6, 1981, "Molecular Interrelations of Nutrition & Cancer." Shamrock Hilton Hotel, Houston. Sponsored by Univ. of Texas System Cancer Center-M.D. Anderson Hospital. Cochairpersons are Marilyn Arnott, Jan van Eys, and Alexander Wang.
16th Annual San Francisco Cancer Symposium—March 13-14, 1981, Hyatt Regency Hotel, "Childhood Cancer: Triump Over Tragedy." Sponsored by West Coast Cancer Foundation, with ACS California Div. Contact WCCF, 50 Francisco St. Suite 200, San Francisco 94133, phone 415-981-4590.
International Conference on Malignant Lymphomas: Current Status & Prospects—Sept. 2-5, 1981, Lugano, Switzerland. Contact F. Cavalli, Head, Div. of Oncology, Ospedale San Giovanni, CH-6500, Bellinzona, Switzerland.
UICC Conference on Clinical Oncology—Oct. 29-31, 1981, Lausanne, Switzerland, in conjunction with the European Society of Medical Oncology. Contact Conference Secretariat, P.O. Box 248, CH 1000, Lausanne 6, Switzerland.

RFA NIH-NIEHS-EP-81-1
National Institute of Environmental Health Sciences

Title: *Alternative designs of standard cancer bioassay*

Application Receipt Date: *Jan. 5, 1981*

Objective of these studies is to stimulate interest in the development of alternative designs of the standard cancer bioassay in order to make the end results more amenable to low-dose extrapolation and risk estimation. In attempting to modify the current bioassay, prospective grant applicants should bear in mind that the overall bioassay is a multiyear, multiphase process and that any or all phases of this process are legitimate subjects for investigation in any attempt to modify the bioassay design. However, any proposed alternative design should maintain the cancer screening potential of the current bioassay. Furthermore, grant applicants should probably regard the present overall total of 600 animals per experiment as an approximate upper bound on experimental size.

Support of this program will be through the NIH traditional grant-in-aid following the guidelines established for this type of support mechanism. While it is expected that each successful applicant will plan, direct and carry out the research program, both the programs and any significant modifications must be mutually agreed upon by the participants and the NIEHS.

It is anticipated that a total of $300,000 will be allocated for this program during the first year; however, award of grants is contingent upon the availability of funds. The project period required to accomplish the aims of the proposal is felt to be two years but meritorious proposals of longer duration will also receive full consideration.

Applications must be responsive to the RFA, and therefore, relevant to the program goals of the sponsoring institute. Those applications considered to be unresponsive to the FDA will be returned to the applicant. Those factors considered to be important for review include: The investigator should be able to demonstrate a knowledge of the various mathematical models/statistical procedures currently employed in low-dose extrapolation, a familiarity with statistical bioassay and experimental design, and some biological background in cancer research. To achieve this background, it may be necessary to adopt a multidisciplinary research team approach. The application will be judged upon the overall scientific merit, ade-

quacy of the methodology, facilities and resources, commitment of time, and cost effectiveness of the proposal.

Applications should be submitted on Form PHS 398. Application kits containing this form and the necessary instructions are available in most institutional business offices or from the Div. of Research Grants, NIH. The original and six copies of the application must be sent to: Div. of Research Grants, National Institutes of Health, Westwood Bldg., Room 240, 5333 Westbard Ave., Bethesda, Md. 20205.

The face page of the application should be labeled "In response to RFA No. NIH-NIEHS-EP-81-1." One copy of the application should be sent to: Dr. Edward Gardner Jr., National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, N.C. 27709.

Questions relating to this announcement may be directed to Gardner at the address above or by phone, 919-755-4021.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the Contracting Officer or Contract Specialist named, Research Contracts Branch, National Cancer Institute, Blair Building, 8300 Colesville Rd., Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CP-FS-11003-77

Title: *Evaluation of nonrandomized screening programs for cervical cancer*

Deadline for statement of capabilities: *Approximately Nov. 20*

NCI proposes to enter into a collaborative contract to develop methodology for the evaluation of nonrandomized screening programs and apply the methodology to cervical cancer screening studies. The approach will focus on quantification of the benefit derived from screening in terms of reduction in mortality and morbidity, and on the relative merit of different screening frequencies. Techniques will be developed for estimating changes in incidence and mortality rates, and the probability of developing invasive and advance stage tumors after one, two or more negative screens. Data to be used in the study will include cervical cancer incidence and mortality prior to and after the introduction of screening in defined populations, screening histories of women, cases of and deaths from cervical cancer outside the screening programs, and general mortality. Parameters will be estimated as a function of screening frequency.

The potential contractor must supply evidence that at least three cervical cancer screening programs, each offering screening at a different frequency, agree to participate in this study. These programs must have begun approximately 15 years ago and must have available cervical cancer morbidity and mortality data for at least 10 years prior to the start of screening. The contractor must have the capability to abstract information from medical and population records, to trace study individuals, and to determine the occurrence of cervical cancer and all major causes of death. Evidence must be provided that experts in disciplines including epidemiology, biostatistics, cytology and gynecology will participate in the study.

Organizations which believe they possess the necessary capabilities and who can meet the criteria listed below must supply the following information:

1. Evidence of the participation in this project of at least three cervical cancer screening programs, each offering Pap smears at a different frequency. These programs should have begun approximately 15 years ago and covered most of a well defined population.

2. Evidence that the participating programs have available morbidity and mortality data for cervical cancer in the target population for at least 10 years prior to the start of screening, and also have available the date and result of each screening visiting for each woman who participated in the screening program. The capability must exist to link cases and deaths with screening history for women in the populations. The ability to identify cervical cancer cases and deaths occurring outside the screening program is also required, as is the identification of all major causes of death in the population.

3. Evidence of staff qualifications in areas of epidemiology and biostatistics, and management of similar studies as requested in the Sources Sought. Curriculum vitae and other appropriate supporting documentation are required.

4. Access to and demonstrated evidence of collaboration with experts in biomedical disciplines required in this study. A list of collaborators and their project involvement for the preceding 12 months will be required.

Ten copies of the capability statement must be submitted.

Contract Specialist: Patrick Williams
Biological Carcinogenesis and Field Studies

The Cancer Letter _Editor Jerry D. Boyd

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